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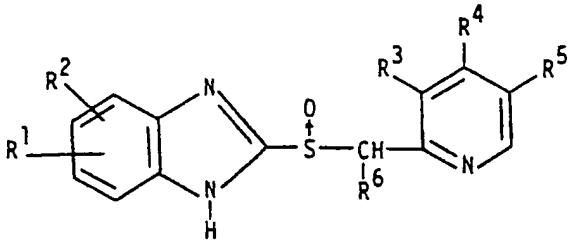
Description

Field of the invention

The present invention is related to new sulphenamide salts having valuable therapeutic properties especially in affecting gastric acid secretion and providing gastrointestinal cytoproptective effect in mammals, including man, as well as processes for the preparation of the new compounds and pharmaceutical compositions comprising them.

Background of the invention

From e.g. EP—A1—0 005 129 sulphoxides of the benzimidazole type of the general formula I



I

in which R^1 and R^2 are the same or different and are hydrogen, alkyl, halogen, methoxycarbonyl, ethoxycarbonyl, alkoxy, or alkanoyl in any position, R^6 is hydrogen, methyl or ethyl, R^3, R^4 and R^5 are the same or different and are each hydrogen, methyl, methoxy, ethoxy, methoxyethoxy or ethoxyethoxy, whereby R^3, R^4 and R^5 are not all hydrogen, and whereby when two of R^3, R^4 and R^5 are hydrogen, the third of R^3, R^4 and R^5 is not methyl, as well as pharmaceutically acceptable salts thereof are known. The compounds of the general formula I can be used in the treatment of gastrointestinal diseases.

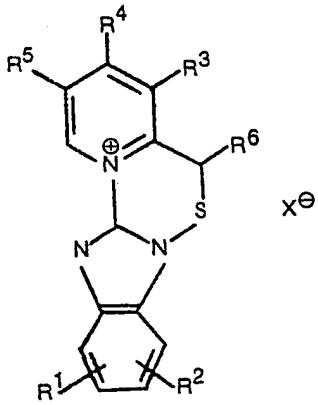
The compounds are known to inhibit gastric acid secretion and have also a gastric cytoprotective effect. Because of their antisecretory effect they may be used in the treatment of peptic ulcer.

The antisecretory activity of the substituted benzimidazoles with the general formula I has been found to be mediated by inhibition of the gastric H^+, K^+-ATPase, the enzyme responsible for the pumping of protons into the stomach. This enzyme is localized in the parietal cells in the gastric mucosa.

The in vivo inhibiting effect of the compounds of the general formula I is not, however, exerted by the compounds as such but by one or more degradation products.

Outline of the invention

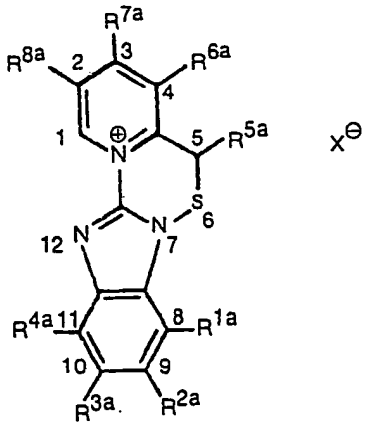
According to the present invention it has now surprisingly been found that the above mentioned degradation reaction of the sulphoxides of the general formula I is a complicated transformation reaction to the new sulphenamides of the general formula III



III

wherein R^1, R^2, R^3, R^4, R^5 and R^6 have the same meaning as given above and X^- is a pharmaceutically acceptable anion.

Compounds of the invention are compounds of the general formula IIIa



IIIa

wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are the same or different and are hydrogen an alkyl, alkoxy, optionally substituted by fluorine or chlorine, halogen, —CN, —CF_3, —NO_2, —COR, —COOR, aryl, aryloxy or arylalkoxy group, or adjacent groups R^{1a}, R^{2a}, R^{3a} and R^{4a} together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring, which rings may be saturated or unsaturated and may contain 0—3 hetero atoms selected from N and O and which rings may be optionally substituted with 1—4 substituents selected from alkyl groups with 1—3 carbon atoms, halogen preferably F or Cl, alkylene radicals containing 4—5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups

$$(—\overset{\overset{O}{\|}}{C}—),$$

whereby if R^{1a}, R^{2a}, R^{3a} and R^{4a} together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, R^{5a} is hydrogen or an alkyl group, R^{6a} is hydrogen or an alkyl group or R^{5a} and R^{6a} are joined together to form an alkenylene chain, R^{7a} is hydrogen, an alkyl, alkoxy, alkenyloxy or alkynyloxy group, R^{8a} is hydrogen or an alkyl group, or R^{6a} and R^{7a}, or R^{7a} and R^{8a} together with the adjacent carbon atoms in the pyridinium ring form a ring wherein the part constituted by R^{6a} and R^{7a} or R^{7a} and R^{8a}, is —O—$(CH_2)_p$—, —$CH_2(CH_2)_p$— or —S—$(CH_2)_p$—, wherein p is 2, 3 or 4 and the O, S and N atoms always are attached to position 3 in the compound IIIa, R is an alkyl, cycloalkyl, aryl or arylalkyl group, and X^- is a pharmaceutically acceptable anion e.g. Cl^-, Br^-, I^-, BF_4^-, PF_6^- or $AuCl_4^-$.

R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a} and R representing an alkyl group is a lower alkyl group having 1—7 carbon atoms, especially preferred 1—4 carbon atoms, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl.

R^{1a}, R^{2a}, R^{3a}, R^{4a} and R^{7a} representing an alkoxy group is a lower alkoxy group having 1—7 carbon atoms, especially preferred 1—3 carbon atoms e.g. methoxy, ethoxy, n-propoxy or isopropoxy.

R^{1a}, R^{2a}, R^{3a} and R^{4a} representing a halogen is chloro, bromo, fluoro or iodo.

R^{1a}, R^{2a}, R^{3a}, R^{4a} and R representing an aryl has up to 10 carbon atoms, especially preferred 6 carbon atoms e.g. phenyl.

R^{1a}, R^{2a}, R^{3a} and R^{4a} representing an aryloxy group has up to 10 carbon atoms, especially preferred 6 carbon atoms, e.g. phenoxy.

R^{1a}, R^{2a}, R^{3a} and R^{4a} representing an arylalkoxy group and R representing an arylalkyl group, have up to 10 carbon atoms in the aryl group and 1—7 carbon atoms in the alkoxy group or the alkyl group, respectively, especially preferred is a group having 6 carbon atoms in the aryl group and 1—3 carbon atoms in the alkoxy group or the alkyl group, respectively, e.g. phenylmethoxy, and phenylmethyl.

R^{5a} and R^{6a} representing an alkenylene chain having 3 carbon atoms, thus forming a quinoline ring is especially preferred.

R^{7a} representing an alkenyloxy or alkynyloxy group has 2—5 carbon atoms, especially preferred 3 carbon atoms.

R representing a cycloalkyl group has 3—10 carbon atoms, especially preferred 3 carbon atoms.

A preferred group of compounds of the general formula IIIa are those wherein at least two or R^{1a}, R^{2a}, R^{3a} and R^{4a} are hydrogen and one or two of the other is a methyl group, R^{5a} is hydrogen, at least one of R^{6a} and R^{8a} is a methyl group and R^{7a} is hydrogen or a methoxy group.

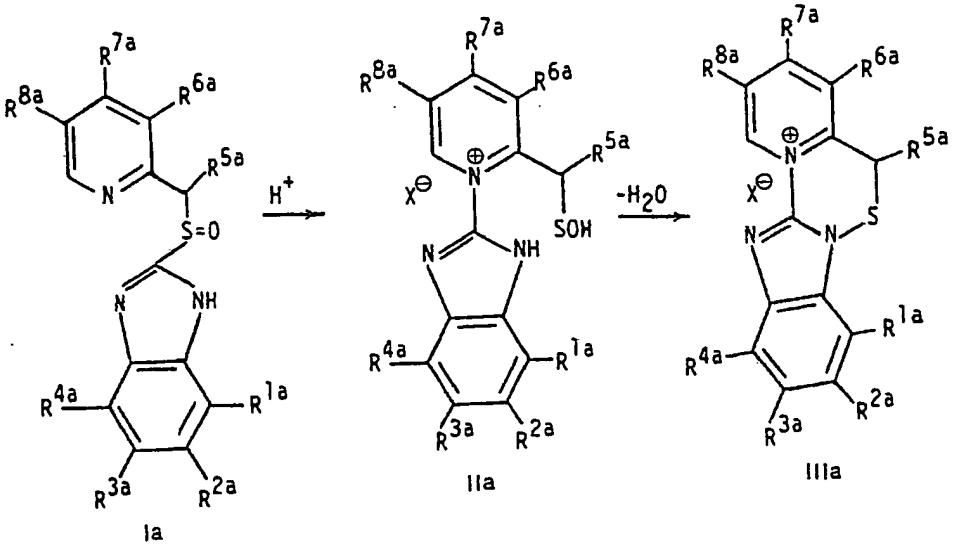
Further preferred compounds of the formula IIIa are the compounds wherein each of R^{1a}, R^{4a}, R^{5a} and R^{8a} is hydrogen, each of R^{2a} and R^{3a} is methyl, R^{7a} is methoxy, R^{6a} is hydrogen or methyl and X^- is BF_4^- and

the compounds, wherein each of R^{1a}, R^{3a}, R^{4a} and R^{5a} is hydrogen, each of R^{6a} and R^{8a} is methyl, R^{7a} is methoxy, R^{2a} is hydrogen or methoxy and X^- is PF_6^- or $AuCl_4^-$.

Especially preferred according to the invention is the isomeric mixture of 2,4 - dimethyl - 3,9 - dimethoxy - 5*H* - pyrido[1',2':4,5][1,2,4]thiadiazino[2,3-*a*]benzimidazol - 13 - ium tetrafluorob rat and 2,4 - dimethyl - 3,10 - dimethoxy - 5*H* - pyrido[1',2':4,5][1,2,4]thiadiaziazino[2,3-*a*]benzimidazol - 13 - ium tetrafluoroborate.

The new compounds of the general formula IIIa according to this invention are potent enzyme inhibitors, primarily inhibitors of the enzyme H^+,K^+-ATPase. In addition, the new compounds exhibit a gastrointestinal cytoprotective effect. In the form of a suitable pharmaceutical composition, the new compounds are therapeutically useful, primarily in the treatment of gastric disorders, such as gastrointestinal inflammatory diseases, including e.g. gastritis, gastric and duodenal ulcer. They may also be used as gastrointestinal cytoprotecting agents.

Compounds of the general formula IIIa above may be prepared according to the following method



The transformation reaction probably goes via the sulphenic acid IIa, which may also be an in vivo inhibitor, when a sulphoxide with the general formula Ia has been adminstered. However, the sulphenic acid is probably not an isolable compound. The transformation from the sulphoxide to the sulphenamide goes via two different pathways, namely

a) one acid catalyzed and

b) one non-acid catalyzed pathway. Both pathways, however, give the same sulphenamide, IIIa.

Especially preferred acids for preparation of the compounds of the general formula IIIa are HPF_6, HBF_4, $HAuCl_4$ and HCl.

The compounds of the general formula Ia, wherein R^{5a} and R^{6a} together form an alkylene chain are new compounds, which form a part of the invention.

Method a)

0.005 mole of a sulphoxide of the general formula Ia is dissolved in 50 ml of 0.2 M HCl in CH_3OH (1 ml of HCl and 49 ml of CH_3OH) at 37°C and is stirred for 7 minutes. (1 ml of acid HPF_6, HBF_4 or $HAuCl_4$) is added and the solution is cooled to 10°C. Crystals of the sulphenamide with the general formula IIIa are precipitated, filtered off and dried.

Method b)

0.005 mole of a sulphoxide of the general formula Ia is dissolved in 50 ml of 0.2 M HCl in CH_3OH (1 ml of HCl and 49 ml of CH_3OH) at 37°C and is stirred for 7 min. The solution is cooled, whereby a sulphenamide with the general formula IIIa is precipitated as its Cl^--salt. The precipitate is filtered off and dried.

Method c)

0.01 mole of a sulphoxide of the general formula Ia is dissolved in 100 ml 0.2M methanolic HBF_4 (2.5 ml 50% HBF_4 and 97.5 ml of CH_3OH) at 37°C and is stirred for 2 min. 50 ml of MeOH is added and the mixture is then stirred for another 3 min at 37°C. The mixture is co led to 5°C. Crystals of the sulphenamide with the general formula IIIa are precipitated, filtered off and dried.

The invention also relates to pharmaceutical compositions containing the new sulphenamides as activ ingredient; to the novel sulphenamides for use in therapy, especially for providing gastrointestinal

cytoprotective effects in mammals and man; to the novel sulphenamides for use in the prevention and treatment of gastrointestinal inflammatory diseases in mammals and man.

For clinical use the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains a compound of the invention in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1—95% by weight of the preparation.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, powdered carrier, e.g. calcium phosphate, lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with lubricating agents e.g. magnesium stearate, calcium stearate, sodium steryl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets. The tablets may be film coated by a suitable film-forming material.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention and a suitable vehicle for soft gelatine capsules. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier e.g. lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

The oral dosage forms may be enteric coated. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To this coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the manner of administration and the disease. In general, oral and parenteral dosages will be in the range of 1 to 400 mg per day of active substance.

Example 1A + 1B

2,4 - Dimethyl - 3,9 - dimethoxy - 5*H* - pyrido[1',2':4,5][1,2,4] - thiadiazino[2,3 - *a*]benzimidazol - 13 - ium tetrafluoroborate (1A) and 2,4 - Dimethyl - 3,10 - dimethoxy - 5*H* - pyrido[1',2':4,5][1,2,4] - thiadiazino[2,3 - *a*]benzimidazol - 13 - ium tetrafluoroborate (1B) (isomeric mixture)

Method a

5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1*H*-benzimidazole (1.72 g, 0.005 mol) was dissolved in 0.2M methanolic HCl (50 ml) (1 ml conc. HCl and 49 ml CH_3OH) and stirred at 37°C for 7 min. Conc. HBF_4 (1 ml) was added and the solution was cooled to 10°C. The desired mixture of the isomeric sulphenamide products was filtered off as a crystalline material and dried. Yield: 1.25 g (60%). NMR. See Table 2.

Method b

5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1*H*-benzimidazole (3.45 g, 0.01 mol) was dissolved in 0.2M methanolic HBF_4 (100 ml) (2.5 ml 50% HBF_4 and 97.5 ml CH_3OH) and stirred at 37°C for 2 min. More methanol (50 ml) was added and the mixture was stirred for another 3 min at 37°C. The mixture was cooled to 5°C, whereupon the desired mixture of isomeric sulphenamide products (1A + 1B) precipitated out. The product in the form of an isomeric mixture was filtered off and dried, yielding 3.3 g (79%). NMR: See Table 2.

Example 11

3-Methoxy-4,9,10-trimethyl-5*H*-pyrido[1',2':4,5][1,2,4]thiadiazino[2,3-*a*]benzimidazol-13-ium chloride (11)

(Method b)

5,6-Dimethyl-2-[[(4-methoxy-3-methyl-2-pyridinyl)methyl]sulphinyl]-1*H*-benzimidazole (1.60 g, 0.005 mol) was dissolved in 0.2M methanolic HCl (50 ml) (1 ml conc. HCl and 49 ml CH_3OH) and stirred at 37° for 7 min. The solution was cooled and the desired sulphenamide salt precipitated. The product was filtered off and dried, yielding 0.3 g (17%). NMR: See Table 2.

Example 12

Benzimidazo[1,2-*b*]pyrido[1,2,3-*de*][1,2,4]benzothiadiazin-14-ium, hexafluorophosphate (12)

(Method a)

2-[8-quinolinyl]-sulphinyl-1*H*-benzimidazole (1.50 g, 0.005 mol) was dissolved in 0.2M methanolic HCl (50 ml) (1 ml conc. HCl and 49 ml CH_3OH) and the soluiton was stirred at 37° for 7 min. Conc. HPF_6 (1 ml) was added and the solution was cooled to 10°C. The desired sulphenamide salt was filtered off as a crystalline material and dried. M.p. 199°C.

The starting compound was prepared according to the following method.

Preparation of 2-[8-quinolinyl]-thio-1*H*-benzimidazole

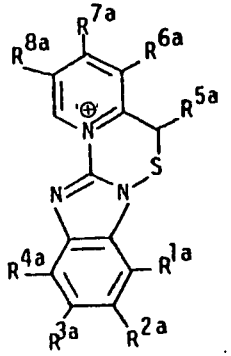
To 8-mercaptoquinoline hydrochloride (5.00 g, 0.025 mol) in ethanol (250 ml) conc. HCl (2.25 ml) and 2-chlorobenzimidazole (3.86 g, 0.025 mol) were added. The mixture was refluxed overnight. pH was adjusted to 13.0 by addition of 2M NaOH. Part of the solvent was evaporated off. The mixture was poured on ice-water. Filtration and recrystallization from CH_3CN gave the desired product (4.50 g, 65%), m.p. 215°C.

Preparation of 2-[8-quinolinyl]-sulphinyl-1*H*-benzimidazole

m-Chloroperbenzoic acid, 82% (3.42 g, 0.016 mol) dissolved in CH_2Cl_2 (100 ml) and cooled to −10°C was added under stirring to 2-[8-quinolinyl]-thio-1*H*-benzimidazole (4.50 g, 0.016 mol) dissolved in CH_2Cl_2 (150 ml) maintaining the temperature at −5°C. Stirring was continued at −5°C for 10 min. The CH_2Cl_2-solution was washed with $NaHCO_3$ (2.69 g, 0.032 mol) dissolved in water (100 ml). The organic phase was dried (Na_2SO_4), filtered and the solvent was evaporated off. CH_3CN was added to the residue and the mixture was warmed under stirring. The precipitate was filtered off and washed with warm CH_3CN, giving the desired product (2.40 g, 51%), m.p. 205°C.

Table 1

Representative examples of compounds included in the scope of the invention.



$X^{\ominus}$ IIIa

Example No.	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	R^{6a}	R^{7a}	R^{8a}	$X^{\ominus}$	Identified by M.p. °C or NMR
1A	H	$-OCH_3$	H	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	BF_4	NMR
1B	H	H	$-OCH_3$	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	BF_4	NMR
2A	H	$-OCH_3$	H	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	NMR
2B	H	H	$-OCH_3$	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	NMR
3A	H	$-OCH_3$	H	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	$AuCl_4$	NMR
3B	H	H	$-OCH_3$	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	$AuCl_4$	NMR
4	H	H	H	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	NMR
5	H	H	H	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	$AuCl_4$	NMR
6	H	H	H	H	H	H	H	H	BF_4	225
7A	H	$-CH_3$	H	H	$-CH_3$	H	H	H	BF_4	NMR
7B	H	H	$-CH_3$	H	$-CH_3$	H	H	H	BF_4	NMR
8	H	$-CH_3$	$-CH_3$	H	$-CH_3$	H	H	H	BF_4	NMR
9	H	$-CH_3$	$-CH_3$	H	H	H	$-OCH_3$	H	BF_4	187

Table 1 cont.

Example No.	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	R^{6a}	R^{7a}	R^{8a}	$X^{\ominus}$	Identified by M.p. °C or NMR
10	H	$-CH_3$	$-CH_3$	H	H	$-CH_3$	$-OCH_3$	H	BF_4	NMR
11	H	$-CH_3$	$-CH_3$	H	H	$-CH_3$	$-OCH_3$	H	Cl	NMR
12	H	H	H	H	=CH-CH=CH-		H	H	BF_4	199
13	H	$-CH_3$	$-CH_3$	H	H	$-CH_3$	H	$-CH_3$	PF_6	NMR
14	H	H	H	H	H	$-CH_3$	$-CH_3$	H	BF_4	215
15	H	H	H	H	H	$-CH_3$	$-CH_3$	H	Cl	170
16	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	Cl	
17	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	
18	H	$-CH_3$	$-CH_3$	$-CH_3$	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	BF_4	
19	H	$-CH_3$	$-CH_3$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	$AuCl_4$	
20	$-CH_3$	H	$-CH_3$	$-CH_3$	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	PF_6	
21	$-CH_3$	H	$-CH_3$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	BF_4	
22	H	H	$-CH_3$	$-CH_3$	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	$AuCl_4$	
23	H	$-CH_3$	$-CH_3$	H	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	Cl	
24	$-CH_3$	H	H	$-CH_3$	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	Cl	
25	H	H	H	$-CH_3$	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	BF_4	
26	H	H	$-CH_3$	H	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	$AuCl_4$	
27	H	H	$-OCH_3$	H	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	PF_6	
28	H	H	$-OCH_3$	H	H	$-CH_3$	$-OCH_2C\equiv CH$	$-CH_3$	Cl	
29	H	H	$-OCH_3$	H	H	$-CH_3$	$-O(CH_2)_3CH=CH_2$	$-CH_3$	$AuCl_4$	
30	H	H	$-OCH_3$	H	H	$-CH_3$	$-O(CH_2)_3CH_3$	$-CH_3$	Cl	
31	H	H	$-OCH_3$	H	H	$-CH_3$	$-OCH(CH_3)_2$	$-CH_3$	PF_6	
32	H	H	$-OCH_3$	H	H	$-CH_3$	$-OC(CH_3)_3$	$-CH_3$	BF_4	

Table 1 (cont.)

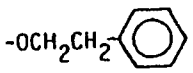
Example No.	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	R^{6a}	R^{7a}	R^{8a}	$X^{\ominus}$	Identified by M.p. °C or NMR
33	H	H	$-OCH_3$	H	H	$-CH_3$	$-OCH_2CH_2CH(CH_3)_2$	$-CH_3$	Cl	
34	H	$-CH_3$	$-OCH_3$	$-CH_3$	H	H	$-CH(CH_3)_2$	$-CH_3$	PF_6	
35	H	$-CH_3$	H	$-CH_3$	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	BF_4	
36	H	H		H	H	$-CH_3$	$-OCH_3$	$-CH_3$	$AuCl_4$	
37	H	H		H	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	
38	H	$-CH_3$	$-COOCH_3$	H	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	BF_4	
39	H	H	$-CH(CH_3)_2$	H	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	Cl	
40	H	H	$-C(CH_3)_3$	H	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	$AuCl_4$	
41	H	$-CH_3$	$-OCH_3$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	BF_4	
42	H	$-CH_3$	$-OCH_3$	$-CH_3$	H	$-CH_3$	$-CH_3$	H	$AuCl_4$	
43	H	$-CH_3$	$-COCH_3$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	
44	H	$-CH_3$	$-COCH_3$	$-CH_3$	H	$-CH_3$	H	$-CH_3$	Cl	
45	H	$-CH_3$	$-COC_2H_5$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	$AuCl_4$	
46	H	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	$-OCH_3$	$-CH_3$	BF_4	
47	H	$-CH_3$	$-CH_3$	$-CH_3$	H	$-CH_3$	$-CH_3$	$-CH_3$	PF_6	
48	H	$-CH_3$	$-C_2H_5$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	Cl	
49	H	$-CH_3$	$-C_2H_5$	$-CH_3$	H	$-CH_3$	$-OCH_3$	H	PF_6	
50	H	$-CH_3$	$-CH(CH_3)_2$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	BF_4	

Table 1 (cont.)

Example No.	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	R^{6a}	R^{7a}	R^{8a}	$X^{\ominus}$	Identified by M.p. °C or NMR
51	H	$-CH_3$	$-CH(CH_3)_2$	$-CH_3$	H	$-CH_3$	$-CH_3$	$-CH_3$	$AuCl_4$	
52	H	$-OCH_3$	-Br	$-OCH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	
53	H	$-OCH_3$	-Br	$-OCH_3$	H	$-CH_3$	$-CH_3$	H	BF_4	
54	H	$-C_2H_5$	-CN	$-C_2H_5$	H	$-CH_3$	$-OCH_3$	H	$AuCl_4$	
55	H	$-C_2H_5$	-CN	$-C_2H_5$	H	$-CH_3$	$-OC_2H_5$	$-CH_3$	Cl	
56	$-CH_3$	$-CH_3$	$-OCH_3$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	Cl	
57	$-CH_3$	H	$-OCH_3$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	BF_4	
58	$-CH_3$	H	$-OCH_3$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	$AuCl_4$	
59	$-OCH_3$	H	$-OCH_3$	-Cl	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	
60	H	-Cl	-Cl	-Cl	H	$-CH_3$	$-OCH_3$	$-CH_3$	Cl	
61	H	$-CH_3$	$-CH_3$	H	H	H	$-OCH_3$	$-C_2H_5$	$AuCl_4$	
62	H	$-CH_3$	$-O(CH_2)_6CH_3$	$-CH_3$	H	$-CH_3$	$-OCH_3$	$-CH_3$	Cl	
63	H	H	$-C_2H_5$	H	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	PF_6	
64	H	H	$-OCH_3$	H	H	$-CH_3$	$-O(CH_2)_2CH(CH_3)_2$	$-CH_3$	BF_4	
65	H	H	$-C(CH_3)_3$	H	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	Cl	
66	H	H		H	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	
67	H	H	$-NO_2$	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	BF_4	
68	H	H	-Br	H	H	$-CH_3$	$-OCH_2CH=CH_2$	$-CH_3$	$AuCl_4$	
69	H	$-CH_3$	$-\overset{O}{\overset{\|}{C}}OCH_3$	H	H	H	$-OCH_3$	$-C_2H_5$	PF_6	

Table 1 (cont.)

Example No.	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	R^{6a}	R^{7a}	R^{8a}	$X^{\ominus}$	Identified by M.p. °C or NMR
70	H	$-CH_3$	$-CH_3$	$-CH_3$	H	$-CH_3$	$-CH_3$	H	BF_4	
71	H	$-CH_3$	$-CH_3$	$-CH_3$	H	H	$-CH_3$	$-CH_3$	Cl	
72	H	$-CH_3$	$-CH_3$	$-CH_3$	H	$-CH_3$	H	$-CH_3$	$AuCl_4$	
73	$-CH_3$	H	$-CH_3$	$-CH_3$	H	$-CH_3$	$-CH_3$	H	BF_4	
74	H	$-CH_3$	-CN	$-CH_3$	H	$-CH_3$	$-OC_2H_5$	$-CH_3$	$AuCl_4$	
75	H	H	$-OCH_3$	H	H	H	$-OCH_3$	$-C_2H_5$	PF_6	
76	H	$-CH_3$	H	$-CH_3$	H	H	$-OCH_2CH=CH_2$	$-CH_3$	Cl	
77	H	H	$-CF_3$	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	$AuCl_4$	
78	H	H	$-NO_2$	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	BF_4	
79	H	H	-Cl	H	H	$-CH_3$	$-OCH_3$	$-CH_3$	PF_6	
80	H	H	H	H	H	$-CH_2CH_2CH_2O-$		H	PF_6	
81	H	OCH_3	H	H	H	$-CH_2CH_2CH_2O-$		H	PF_6	
82	H	H	H	H	H	$-CH_2CH_2CH_2CH_2-$		H	Cl	
83	H	OCH_3	H	H	H	$-CH_2CH_2CH_2CH_2-$		H	BF_4	
84	H	H	H	H	H	$-CH_2CH_2CH_2S-$		H	PF_6	
85	H	OCH_3	H	H	H	H	$-CH_2CH_2CH_2CH_2-$		PF_6	
86	H	$-OCF_2CHFO-$		H	H	CH_3	OCH_3	H	PF_6	
87	H	$-OCF_3CHFO-$		H	H	H	OCH_3	H	PF_6	
88	H	$-OCF_2O-$		H	H	CH_3	OCH_3	H	Br	
89	H	$-OCF_2O-$		H	H	H	OCH_3	H	Cl	
90	H	$-OCF_2O-$		H	H	H	OCH_3	CH_3	Cl	
91	H	$-OCF_2CFClO-$		H	H	CH_3	OCH_3	H	BF_4	
92	H	-CO- 	H	H	H	CH_3	OCH_3	H	Cl	

Table 1 (cont.)

Example No.	R^{1a}	R^{2a}	R^{3a}	R^{4a}	R^{5a}	R^{6a}	R^{7a}	R^{8a}	$X^{\ominus}$	Identified by M.p. °C or NMR
93	H		H	H	H	H	OCH_3	H	I	
94	H		H	H	H	CH_3	OCH_3	H	BF_4	
95	H	OCF_3	H	H	H	CH_3	OCH_3	H	PF_6	
96	H	OCF_3	H	H	H	H	OCH_3	H	Cl	
97	H	OCF_3	H	H	H	H	OCH_3	CH_3	PF_6	
98	H	OCF_3	H	H	H	CH_3	OCH_3	CH_3	Cl	
99	H	OCF_2CHF_2	H	H	H	CH_3	OCH_3	H	Br	
100	H	OCF_2CHF_2	H	H	H	H	OCH_3	H	Cl	
101	H	OCF_2CHF_2	H	H	H	H	OCH_3	CH_3	PF_6	
102	H	OCH_2CF_3	H	H	H	CH_3	OCH_3	H	PF_6	
103	H	$OCHF_2$	H	H	H	CH_3	OCH_3	H	PF_6	
104	H	$OCHF_2$	$OCHF_2$	H	H	H	OCH_3	H	PF_6	
105	H	$OCHF_2$	OCH_3	H	H	CH_3	OCH_3	H	PF_6	

Identifying data for the compounds according to the examples 1—5, 7, 8, 10, 11 and 13 are given in the following table 2.

Table 2.

Compound according to example	NMR data (90 MHz) δ ppm (CD_3CN)
1 A } isomeric mixture 1 B }	2.53(s,3H), 2.63(s,3H), 3.97(s,3H), 4.37(s,3H), 4.90(s,2H), 6.97-7.83(m,3H), 9.30(s,1H)
2 A } isomeric mixture 2 B }	2.53(s,3H), 2.63(s,3H), 3.93(s,3H), 4.37(s,3H), 4.90(s,2H), 7.0-7.83(m,3H), 9.30(s,1H)
3 A } isomeric mixture 3 B }	2.50(s,3H), 2.60(s,3H), 3.90(s,3H), 4.30(s,3H), 4.83(s,2H), 7.0-7.80(m,3H), 9.30(s,1H)
4	2.50(s,3H), 2.63(s,3H), 4.37(s,3H), 4.87(s,2H), 7.30-7.60(m,3H), 7.6-8.0(m,1H), 9.37(s,1H)
5	2.47(s,3H), 2.60(s,3H), 4.33(s,3H), 4.87(s,2H), 7.10-7.70(m,3H), 7.73-8.0(m,1H), 9.37(s,1H)
7 A } isomeric mixture 7 B }	1.57(d,3H), 2.50 and 2.53 (2s, totally 3H), 5.20(q,1H), 7.27-7.50(m,2H), 7.60-7.83(m,1H), 8.13-8.33(m,2H), 8.70-8.97(m,1H), 9.67(d,1H)
8	1.60(d,3H), 2.47(s,3H), 2.50(s,3H), 5.23(q,1H), 7.50(s,1H), 7.77(s,1H), 8.33(s,1H), 8.43(s,1H), 8.90(d,1H), 9.80(d,1H)
10	2.46(s,9H), 4.30(s,3H), 4.83(s,2H), 7.40-7.80 (m,3H), 9.50(d,1H)
11	2.43(s,6H), 2.47(s,3H), 4.30(s,3H), 4.97(s,2H), 7.20(s,2H), 7.40(d,1H), 9.50(d,1H)
13	2.43(s,3H), 2.50(s,3H), 2.63(s,3H), 2.70(s,3H), 4.90(s,2H), 7.50(s,1H), 7.70(s,1H), 8.60(s,1H), 9.47(s,1H)

Incorporation of the new sulphenamides of the present invention in pharmaceutical preparations is exemplified by the following example.

Example 106

Tablets

3-Methoxy-4,9,10-trimethyl-5-*H*-pyrido[1',2':4,5][1,2,4]thiadiazino[2,3-*a*]-benzimidazol-13-ium chloride (250 g), was mixed with

500 g lactose anhydrous

500 g microcrystalline cellulose

100 g crosslinked polyvinylpoyrrolidone

in a mixer. 5 g of magnesium stearate was admixed and the mixture was pressed into tablets each weighing 275 mg.

Biological tests

I. *In vitro* inhibition of gastric H^+,K^+-ATPase

Hog gastric H^+,K^+-ATPase was purified according to Saccomani et al., Biochim. Biophys. Acta 465, 311—330, 1977. 10 µg of membrane protein (GI-fraction in the reference listed above) was incubated with 2 mmol/l of piperazine-N,N'-bis-(2-ethane sulfonic acid) buffer pH 7,4 and the test compound in concentrations 10^{-7}—10^{-4}M in a final volume of 1 ml. (The test compound was dissolved in methanol. Aliquots of these stock solutions were diluted to a final methanol concentration below 1%, which on its own had no effect on the enzyme activities). After 30 minutes of incubation, the remaining H^+,K^+-ATPase activity was determined, according to Wallmark et al., Biochim. Biophys. Acta, 728, 31—38, 1983. A dose-response curve was constructed and the concentration at half-maximal inhibition (IC_{50}) could be determined. When testing the isomeric mixture from Examples 1A and 1B an $IC_{50} = 6.10^{-7}$M was obtained.

II. Inhibiting effect *in vivo* on gastric acid secretion in conscious dog

Test Method

Chronic gastric fistula dogs were used. These dogs have been surgically provided with a gastric cannula in the stomach and a duodenal fistula used for direct intraduodenal administration of test compounds. Following a 4 weeks' recovery period after surgery, tests were performed once a week on each dog. Food and water were withdrawn 18 hours before each test.

The test compound was suspended in 0.5% Methocel® (90 HG, 15.000, Dow Chem Corp.), the pH was immediately adjusted to about 4 by addition of hydrochloric acid and the suspension administered orally by using a stomach tube. After 1 hour gastric acid secretion was induced by continuous infusion of histamine at individual doses (400—600 nmol/kg, h), resulting in approx. 90% of maximal secretion of gastric acid. The gastric juice was collected by free flow from the gastric cannula in consecutive 30 minutes samples for 2 hours. The samples were titrated to pH 7.0 with 0.1 M NaOH using a Radiometer automatic titrator and the acid output was calculated. The per cent inhibition of acid secretion was calculated by comparing in each dog the acid output in the tests to the acid output in control tests when only the vehicle was given. The peak inhibitory effect for each compound was determined. When testing the isomeric mixture from Examples 1A and 1B at a concentration of 4 µmol/kg an inhibition of 40% was obtained.

III. In vivo cytoprotective effect: Effect on ethanol-induced gastric lesions in the rat

Two groups of female Spraque-Dawley rats (190—220 g) were used, one for the test compound and one for the control experiment. Food, but not water, was removed 24 h before the experiments.

The animals in the test group were treated orally with the test compound dissolved in 0.01 M HCl immediately before the test and the animals in the control group were given the vehicle (0.01 M HCl) in a dose of 1 ml/kg.

Five or thirty minutes later the rats were given orally 1 ml of absolute ethanol (a standard agent for inducing gastric mucosal lesions).

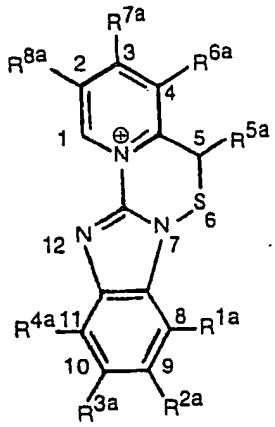
Thirty minutes later the rats were killed by carbon dioxide asphyxiation, their stomachs dissected out and the gastric mucosae were examined for the presence of necrotic lesions. The total lengths of the lesions in the stomachs were measured in the test group and in the control group, in both cases treated five and thirty minutes before with ethanol.

When testing the isomeric mixture from Example 1A and 1B at a dose of 20 µmol/kg the total lengths of lesions in the stomachs were reduced to 5.3 cm (5 min) and 4.4 cm (30 min) compared to the lesions of the controls, which were 11.4 cm (5 min) and 10.4 cm (30 min). This indicates an ED_{50}-value below 20 µmol/kg.

The biological tests thus show that the compounds of the general formula IIIa both inhibit gastric acid secretion and have a gastrointestinal cytoprotecting effect.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula IIIa



IIIa

wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are the same or different and are hydrogen, an alkyl group having 1—7 carbon atoms, an alkoxy group having 1—7 carbon atoms optionally substituted by fluorine or chlorine, halogen, —CN, —CF_3, —NO_2, —COR, —COOR, an aryl group having up to 10 carbon atoms, an aryloxy group having up to 10 carbon atoms in the aryl group and 1—7 carbon atoms in the alkoxy group, or adjacent groups R^{1a}, R^{2a}, R^{3a} and R^{4a} together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring, which rings may be saturated or unsaturated and may contain 0—3 heteroatoms selected from N and O and which rings may be optionally substituted with 1—4 substituents selected from alkyl groups with 1—3 carbon atoms, halogen preferably F or Cl, alkylene radicals containing 4—5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups

whereby if R^{1a}, R^{2a}, R^{3a} and R^{4a} together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, R^{5a} is hydrogen or an alkyl group having 1—7 carbon atoms, R^{6a} is hydrogen or an alkyl group having 1—7 carbon atoms or R^{5a} and R^{6a} are joined together to form an alkenylene chain having 3 carbon atoms, R^{7a} is hydrogen, an alkyl group having 1—7 carbon atoms, an alkoxy group having 1—7 carbon atoms, an alkenyloxy or alkynyloxy group each having 2—5 carbon atoms, R^{8} is hydrogen or an alkyl group having 1—7 carbon atoms, or R^{6a} and R^{7a}, or R^{7a} and R^{8a} together with the adjacent carbon atoms in the pyridinium ring form a ring wherein the part constituted by R^{6a} and R^{7a} or R^{7a} and R^{8a}, is —O—$(CH_2)_p$—, —$CH_2(CH_2)_p$— or —S—$(CH_2)_p$—, wherein p is 2, 3 or 4 and the O, S and N atoms always are attached to position 3 in the compound IIIa, R is an alkyl group having 1—7 carbon atoms, a cycloalkyl group having 3—10 carbon atoms, an aryl group having up to 10 carbon atoms or an arylalkyl group having up to 10 carbon atoms in the aryl and 1—7 carbon atoms in the alkyl, and $X^{\ominus}$ is a pharmaceutically acceptable anion.

2. A compound according to claim 1, wherein the pharmaceutically acceptable anion is Cl^-, Br^-, I^-, PF_6^- or $AuCl_4^-$.

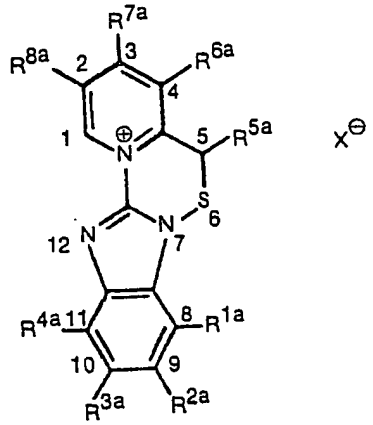
3. A compound according to claims 1—2 wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are the same or different and are each hydrogen, a lower alkyl group having 1—4 carbon atoms, a lower alkoxy group having 1—3 carbon atoms, chloro, bromo, fluoro or iodo, an aryl group having 6 carbon atoms, an aryloxy group having 6 carbon atoms, an aralkoxy group having 6 carbon atoms in the aryl group and 1—3 carbon atoms in the alkoxy group, —COR and/or —COOR, wherein R is a lower alkyl group having 1—4 carbon atoms, a cycloalkyl having 3 carbon atoms, an aryl having 6 carbon atoms or an arylalkyl group having 6 carbon atoms in the aryl group and 1—3 carbon atoms in the alkyl group, R^{5a} is hydrogen or a lower alkyl group having 1—4 carbon atoms, R^{6a} is hydrogen or a lower alkyl group having 1—4 carbon atoms or R^{5a} and R^{6a} are joined together to form an alkenylene chain having 3 carbon atoms, R^{7a} is hydrogen, a lower alkyl group having 1—4 carbon atoms, an alkoxy group having 1—3 carbon atoms, an alkenyloxy or an alkynyloxy group each having 3 carbon atoms and R^{8a} is hydrogen or a lower alkyl group having 4 carbon atoms.

4. A compound according to claims 1—3 wherein each of R^{1a}, R^{4a}, R^{5a} and R^{8a} is hydrogen, each of R^{2a} and R^{3a} is methyl, R^{7a} is methoxy, R^{6a} is hydrogen or methyl and X^- is BF_4^-.

5. A compound according to claims 1—3 wherein each of R^{1a}, R^{3a}, R^{4a} and R^{5a} is hydrogen, each of R^{6a} and R^{8a} is methyl, R^{7a} is methoxy, R^{2a} is hydrogen or methoxy and X^- is PF_6^- or $AuCl_4^-$.

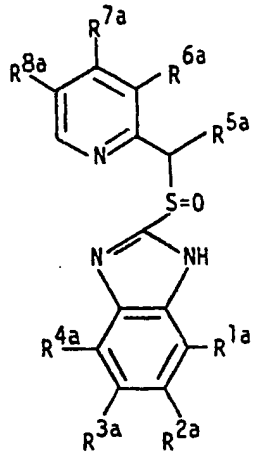
6. The isomeric mixture of 2,4 - dimethyl - 3,9 - dimethoxy - 5*H* - pyrido - [1',-2':4,5][1,2,4] - thiadiazino[2,3 - a] benzimidazol - 13 - ium tetrafluoroborate and 2,4 - dimethyl - 3,10 - dimethoxy - 5*H* - pyrido[1',2':4,5][1,2,4]thiadiazino - [2,3 - *a*] benzimidazol - 13 - ium tetrafluoroborate.

7. A process for the preparation of a compound of the formula IIIa



IIIa

wherein R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a} and R^{8a} and $X^{\ominus}$ are as defined in claim 1, characterized by reacting under transformation and acidic conditions of a compound of the general formula Ia



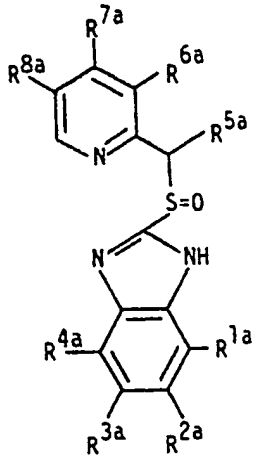
Ia

either a) acid catalyzed or b) non-acid catalyzed to form the salt of the formula IIIa.

8. A process according to claim 7 wherein the reaction is catalyzed by an acid.

9. A process according to claim 7 and 8 wherein the reaction is catalyzed by HPF_6, HBF_4 or $HAuCl_4$.

10. A compound with the general formula Ia



Ia

wherein R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{7a} and R^{8a} are as defined in claim 1 and R^{5a} and R^{6a} are joined together under the formation of an alkenylene chain having 3 carbon atoms.

11. A pharmaceutical composition containing as active ingredient a compound according to any of the claims 1—6.

12. A compound as defined in any of the claims 1—6 for use in inhibiting gastric acid secretion in mammals and man.

13. A compound as defined in any of the claims 1—6 for use as gastrointestinal cytoprotecting agent in mammals and man.

14. A compound as defined in any of the claims 1—6 for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.

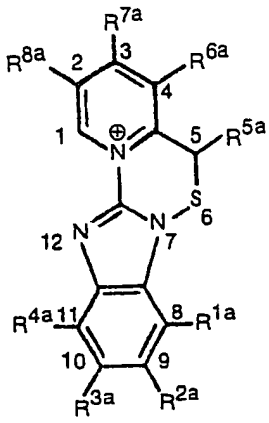
15. Use of a compound of the general formula IIIa according to claim 1 for the manufacture of a pharmaceutical preparation for inhibiting gastric acid secretion.

16. Use of a compound of the general formula IIIa according to claim 1 for the manufacture of a pharmaceutical preparation for treatment of gastrointestinal inflammatory diseases.

17. Use of a compound of the general formula IIIa according to claim 1 for the manufacture of a pharmaceutical preparation having gastrointestinal cytoprotective effect.

Claims for the Contracting State: AT

1. A process for the preparation of a compound of the formula IIIa

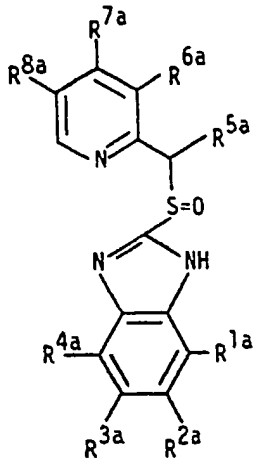


IIIa

wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are the same or different and are hydrogen, an alkyl group having 1—7 carbon atoms, an alkoxy group having 1—7 carbon atoms optionally substituted by fluorine or chlorine, halogen, —CN, —CF_3, —NO_2, —COR, —COOR, an aryl group having up to 10 carbon atoms, an aryloxy group having up to 10 carbon atoms or an arylalkoxy group having up to 10 carbon atoms in the aryl group and 1—7 carbon atoms in the alkoxy group, or adjacent groups R^{1a}, R^{2a}, R^{3a} and R^{4a} together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring, which rings may be saturated or unsaturated and may contain 0—3 heteroatoms selected from N and O and which rings may be optionally substituted with 1—4 substituents selected from alkyl groups with 1—3 carbon atoms, halogen preferably F or Cl, alkylene radicals containing 4—5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups

whereby if R^{1a}, R^{2a}, R^{3a} and R^{4a} together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, R^{5a} is hydrogen or an alkyl group having 1—7 carbon atoms, R^{6a} is hydrogen or an alkyl group having 1—7 carbon atoms or R^{5a} and R^{6a} are joined together to form an alkylene chain having 3 carbon atoms, R^{7a} is hydrogen, an alkyl group having 1—7 carbon atoms, an alkoxy group having 1—7 carbon atoms, an alkenyloxy or alkynyloxy group each having 2—5 carbon atoms, R^8 is hydrogen or an alkyl group having 1—7 carbon atoms, or R^{6a} and R^{7a}, or R^{7a}, R^{8a} together with the adjacent carbon atoms in the pyridinium ring form a ring wherein the part constituted by R^{6a} and R^{7a} or R^{7a} and R^{8a} is —O—$(CH_2)_p$—, —$CH_2(CH_2)_p$— or —S—$(CH_2)_p$—, wherein p is 2, 3 or 4 and the O, S and N atoms always are attached to position 3 in the compound IIIa, R is an alkyl group having 1—7 carbon atoms, a cycloalkyl group having 3—10 carbon atoms, an aryl group having up to 10 carbon atoms or an arylalkyl group having up to 10 carbon atoms in the aryl and 1—7 carbon atoms in the alkyl, and $X^{\ominus}$ is a pharmaceutically

acceptable anion, characterized by reacting under transformation and acidic conditions of a compound of the general formula Ia



Ia

either a) acid catalyzed or b) non-acid catalyzed to form the salt of the formula IIIa.

2. A process according to claim 1, wherein the pharmaceutically acceptable anion is Cl^-, Br^-, I^-, BF_4^-, PF_6^- or $AuCl_4^-$.

3. A process according to claims 1—2 wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are the same or different and are each hydrogen, a lower alkyl group having 1—4 carbon atoms, a lower alkoxy group having 1—3 carbon atoms, chloro, bromo, fluoro or iodo, an aryl group having 6 carbon atoms, an aryloxy group having 6 carbon atoms, an aralkoxy group having 6 carbon atoms in the aryl group and 1—3 carbon atoms in the alkoxy group, —COR and/or —COOR, wherein R is a lower alkyl group having 1—4 carbon atoms, a cycloalkyl having 3 carbon atoms, an aryl having 6 carbon atoms or an arylalkyl group having 6 carbon atoms in the aryl group and 1—3 carbon atoms in the alkyl group, R^{5a} is hydrogen or a lower alkyl group having 1—4 carbon atoms, R^{6a} is hydrogen or a lower alkyl group having 1—4 carbon atoms or R^{5a} and R^{6a} are joined together to form an alkenylene chain having 3 carbon atoms, R^{7a} is hydrogen, a lower alkyl group having 1—4 carbon atoms, an alkoxy group having 1—3 carbon atoms, an alkenyloxy or an alkynyloxy group each having 3 carbon atoms and R^{8a} is hydrogen or a lower alkyl group having 4 carbon atoms.

4. A process according to claims 1—3 wherein each of R^{1a}, R^{4a}, R^{5a} and R^{8a} is hydrogen, each of R^{2a} and R^{3a} is methyl, R^{7a} is methoxy, R^{6a} is hydrogen or methyl and X^- is BF_4^-.

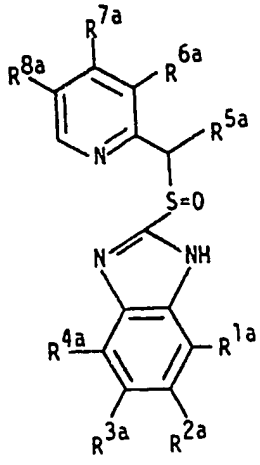
5. A process according to claims 1—3 wherein each of R^{1a}, R^{3a}, R^{4a} and R^{5a} is hydrogen, each of R^{6a} and R^{8a} is methyl, R^{7a} is methoxy, R^{2a} is hydrogen or methoxy and X^- is PF_6^- or $AuCl_4^-$.

6. The process according to claim 1, wherein the isomeric mixture of 2,4 - dimethyl - 3,9 - dimethoxy - 5*H* - pyrido - [1′,2′:4,5][1,2,4] - thiadiazino[2,3 - a] benzimidazol - 13 - ium tetrafluoroborate and 2,4 - dimethyl - 3,10 - dimethoxy - 5*H* - pyrido[1′,2′:4,5][1,2,4]thiadiazino - [2,3 - *a*] benzimidazol - 13 - ium tetrafluoroborate is prepared.

7. A process according to claim 1 wherein the reaction is catalyzed by an acid.

8. A process according to claim 1 and 7 wherein the reaction is catalyzed by HPF_6, HBF_4 or $HAuCl_4$.

9. A process according to claim 1 wherein a compound with the general formula Ia



Ia

wherein R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{7a} and R^{8a} are as defined in claim 1 and R^{5a} and R^{6a} are joined together under the formation of an alkyenylene chain having 3 carbon atoms is used as the starting compound.

10. A process for the preparation of a pharmaceutical composition containing as active ingredient a compound according to any of the claims 1—6, characterized in that the active compound of the formula IIIa is mixed with one or more carriers to a pharmaceutical composition.

11. A process according to any of the claims 1—8, wherein the compound obtained is for use in inhibiting gastric acid secretion in mammals and man.

12. A process according to any of the claims 1—8, wherein the compound obtained is for use as gastrointestinal cytoprotecting agent in mammals and man.

13. A process according to any of the claims 1—8, wherein the compound obtained is for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.

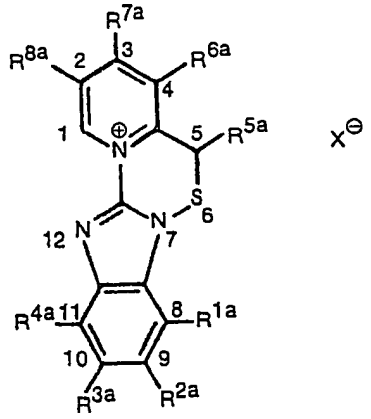
14. Use of a compound af the general formula IIIa according to claim 1 for the manufacture of a pharmaceutical preparation for inhibiting gastric acid secretion.

15. Use of a compound of the general formula IIIa according to claim 1 for the manufacture of a pharmaceutical preparation for treatment of gastrointestinal inflammatory diseases.

16. Use of a compound of the general formula IIIa according to claim 1 for the manufacture of a pharmaceutical preparation having gastrointestinal cytoprotective effect.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der Formel IIIa



IIIa

worin R^{1a}, R^{2a}, R^{3a} und R^{4a} gleich oder verschieden sind und Wasserstoff, eine Alkylgruppe mit 1—7 Kohlenstoffatomen, eine Alkoxygruppe mit 1—7 Kohlenstoffatomen, gegebenenfalls durch Fluor oder Chlor substituiert, Halogen, —CN, —CF_3, —NO_2, —COR, —COOR, eine Arylgruppe mit bis zu 10 Kohlenstoffatomen, eine Aryloxygruppe mit bis zu 10 Kohlenstoffatomen oder eine Arylalkoxygruppe mit bis zu 10 Kohlenstoffatomen in der Arylgruppe und 1—7 Kohlenstoffatomen in der Alkoxygruppe bedeuten, oder benachbarte Gruppen R^{1a}, R^{2a}, R^{3a} und R^{4a} zusammen mit den benachbarten Kohlenstoffatomen im Benzimidazolring einen 5-, 6- oder 7-gliedrigen monocyclischen Ring bilden, welche Ringe gesättigt oder ungesättigt sein können und 0—3 Heteroatome, ausgewählt aus N und O, enthalten können, und welche Ringe gegebenenfalls durch 1—4 Substituenten, ausgewählt aus Alkylgruppen mit 1—3 Kohlenstoffatomen, Halogen, vorzugsweise F oder Cl, Alkylengruppen mit 4—5 Kohlenstoffatomen, die Spiroverbindungen liefern, substituiert sein können, oder zwei oder vier dieser Substituenten zusammen eine oder zwei Oxogruppen

bilden, wobei R^{1a}, R^{2a}, R^{3a} und R^{4a}, wenn sie zusammen mit dem benachbarten Kohlenstoffatom im Benzimidazolring zwei Ringe bilden, miteinander kondensiert werden können, R^{5a} Wasserstoff oder eine Alkylgruppe mit 1—7 Kohlenstoffatomen ist, R^{6a} für Wasserstoff oder eine Alkylgruppe mit 1—7 Kohlenstoffatomen steht, oder R^{5a} und R^{6a} zur Bildung einer Alkenylenkette mit 3 Kohlenstoffatomen vereinigt sind, R^{7a} Wasserstoff, eine Alkylgruppe mit 1—7 Kohlenstoffatomen, eine Alkoxygruppe mit 1—7 Kohlenstoffatomen, eine Alkenyloxy- oder Alkynyloxygruppe mit jeweils 2—5 Kohlenstoffatomen ist, R^{8} für Wasserstoff oder eine Alkylgruppe mit 1—7 Kohlenstoffatomen steht, oder R^{8a} und R^{7a} oder R^{7a} und R^{8a} zusammen mit den benachbarten Kohlenstoffatomen im Pyridiniumring einen Ring bilden, worin der durch R^{8a} und R^{7a} oder R^{7a} und R^{8a} gebildete Teil —O—$(CH_2)_p$—, —$CH_2(CH_2)_p$— oder —S—$(CH_2)_p$— bedeutet, worin p für 2, 3 oder 4 steht und die O-, S- und N-Atome immer an der Position 3 in der Verbindung IIIa stehen, R eine Alkylgruppe mit 1—7 Kohlenstoffatomen, eine Cycloalkygruppe mit 3—10 Kohlenstoff-

atomen, eine Arylgruppe mit bis zu 10 Kohlenstoffatomen oder eine Arylalkylgruppe mit bis zu 10 Kohlenstoffatomen im Aryl und 1—7 Kohlenstoffatomen im Alkyl darstellt und $X^{\ominus}$ ein pharmazeutisch akzeptables Anion ist.

2. Verbindung nach Anspruch 1, worin das pharmazeutisch akzeptable Anion Cl^-, Br^-, I^-, PF_6 oder $AuCl_4^-$ ist.

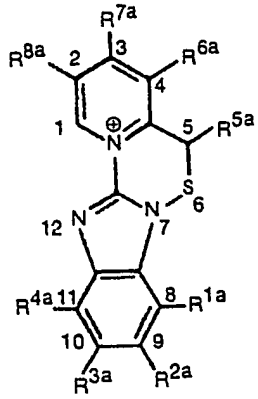
3. Verbindung nach den Ansprüchen 1—2, worin R^{1a}, R^{2a}, R^{3a} und R^{4a} gleich oder verschieden sind und jeweils für Wasserstoff, eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen, eine Niedrigalkoxygruppe mit 1—3 Kohlenstoffatomen, Chlor, Brom, Fluor oder Jod, eine Arylgruppe mit 6 Kohlenstoffatomen, eine Aryloxygruppe mit 6 Kohlenstoffatomen, eine Aralkoxygruppe mit 6 Kohlenstoffatomen in der Arylgruppe und 1—3 Kohlenstoffatomen in der Alkoxygruppe, —COR und/oder —COOR stehen, worin R eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen, ein Cycloalkyl mit 3 Kohlenstoffatomen, ein Aryl mit 6 Kohlenstoffatomen oder eine Arylalkylgruppe mit 6 Kohlenstoffatomen in der Arylgruppe und 1—3 Kohlenstoffatomen in der Alkylgrupe ist, R^{5a} Wasserstoff oder eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen darstellt, R^{6a} Wasserstoff oder eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen ist, oder R^{5a} und R^{6a} zur Bildung einer Alkenylenkette mit 3 Kohlenstoffatomen vereinigt sind, R^{7a} Wasserstoff, eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen, eine Alkoxygruppe mit 1—3 Kohlenstoffatomen, eine Alkenyloxy- oder eine Alkynyloxygruppe mit jeweils 3 Kohlenstoffatomen darstellt und R^{8a} Wasserstoff oder eine Niedrigalkylgruppe mit 4 Kohlenstoffatomen ist.

4. Verbindung nach den Ansprüchen 1—3, worin jedes von R^{1a}, R^{4a}, R^{5a} und R^{8a} für Wasserstoff steht, jedes von R^{2a} und R^{3a} Methyl ist, R^{7a} Methoxy bedeutet, R^{6a} Wasserstoff oder Methyl ist und X^- für BF_4^- steht.

5. Verbindung nach den Ansprüchen 1—3, worin jedes von R^{1a}, R^{3a}, R^{4a} und R^{5a} Wasserstoff ist, jedes von R^{6a} und R^{8a} Methyl darstellt, R^{7a} Methoxy bedeutet, R^{2a} Wasserstoff oder Methoxy ist und X^- für PF_6^- oder $AuCl_4^-$ steht.

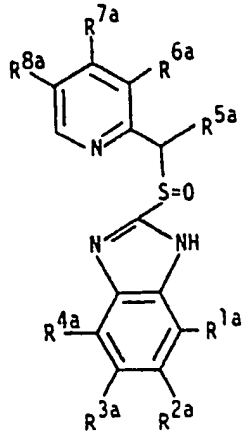
6. Isomerenmischung von 2,4 - Dimethyl - 3,9 - dimethoxy - 5*H* - pyrido - [1',2':4,5] - [1,2,4] - thiadiazino - [2,3 - a] - benzimidazol - 13 - ium - tetrafluorborat und 2,4 - Dimethyl - 3,10 - dimethoxy - 5*H* - pyrido - [1',2':4:5] - [1,2,4] - thiadiazino - [2,3 - a] - benzimidazol - 13 - ium - tetrafluorborat.

7. Verfahren zur Herstellung einer Verbindung der Formel IIIa



IIIa

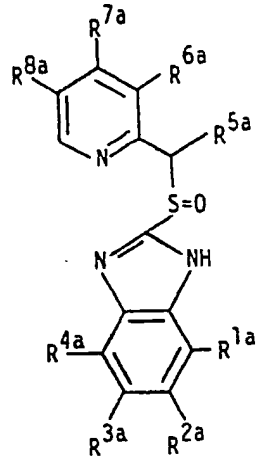
worin R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a} und R^{8a} und $X^{\ominus}$ wie in Anspruch 1 definiert sind, gekennzeichnet durch Umsetzung unter Umwandlung und sauren Bedingungen einer Verbindung der allgemeinen Formel Ia



Ia

entweder a) säurekatalysiert oder b) nicht säurekatalysiert, zur Bildung des Salzes der Formel IIIa.

8. Verfahren nach Anspruch 7, worin die Reaktion mit einer Säure katalysiert wird.
9. Verfahren nach Anspruch 7 und 8, worin die Reaktion mit HPF_6, HBF_4 oder $HAuCl_4$ katalysiert wird.
10. Verbindung der allgemeinen Formel Ia



Ia

worin R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{7a} und R^{8a} wie in Anspruch 1 definiert sind und R^{5a} und R^{6a} unter Bildung einer Alkenylenkette mit 3 Kohlenstoffatomen vereinigt sind.

11. Pharmazeutische Zusammensetzung, die als aktives Ingrediens eine Verbindung nach einem der Ansprüche 1—6 enthält.

12. Verbindung nach einem der Ansprüche 1—6 zur Verwendung bei der Inhibition von Magensäuresekretion bei Säugetieren und Menschen.

13. Verbindung nach einem der Ansprüche 1—6 zur Verwendung als gastrointestinales zellschützendes Mittel bei Säugetieren und Menschen.

14. Verbindung nach einem der Ansprüche 1—6 zur Verwendung bei der Behandlung von gastrointestinalen Entzündungserkrankungen bei Säugetieren und Menschen.

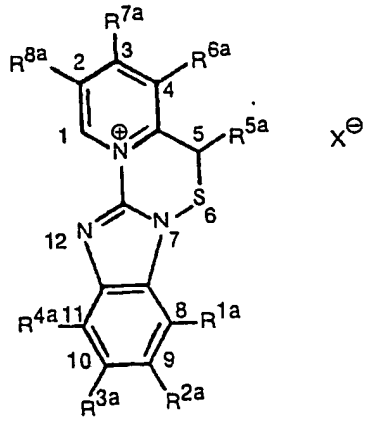
15. Verwendung einer Verbindung der allgemeinen Formel IIIa nach Anspruch 1 zur Herstellung einer pharmazeutischen Präparation zur Inhibition von Magensäuresekretion.

16. Verwendung einer Verbindung der allgemeinen Formel IIIa nach Anspruch 1 zur Herstellung einer pharmazeutischen Präparation zur Behandlung von gastrointestinalen Entzündungserkrankungen.

17. Verwendung einer Verbindung der allgemeinen Formel IIIa nach Anspruch 1 zur Herstellung einer pharmazeutischen Präparation mit gastrointestinaler Zellschutzwirkung.

Patentansprüche für den Vertragsstaat: AT

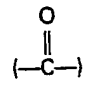
1. Verfahren zur Herstellung einer Verbindung der Formel IIIa



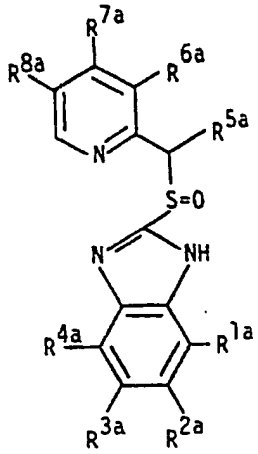
IIIa

worin R^{1a}, R^{2a}, R^{3a} und R^{4a} gleich oder verschieden sind und Wasserstoff, eine Alkylgruppe mit 1—7 Kohlenstoffatomen, eine Alkoxygruppe mit 1—7 Kohlenstoffatomen, gegebenenfalls durch Fluor oder Chlor substituiert, Halogen, —CN, $—CF_3$, $—NO_2$, —COR, —COOR, eine Arylgruppe mit bis zu 10 Kohlenstoffatomen, eine Aryloxygruppe mit bis zu 10 Kohlenstoffatomen oder eine Arylalkoxygruppe mit bis zu 10 Kohlenstoffatomen, in der Arylgruppe und 1—7 Kohlenstoffatomen in der Alkoxygruppe bedeuten, oder

benachbarte Gruppen R^{1a}, R^{2a}, R^{3a} und R^{4a} zusammen mit den benachbarten Kohlenstoffatomen im Benzimidazolring einen 5-, 6- oder 7-gliedrigen monocyclischen Ring bilden, welche Ringe gesättigt oder ungesättigt sein können und 0—3 Heteroatome, ausgewählt aus N und O, enthalten können, und welche Ringe gegebenenfalls durch 1—4 Substituenten, ausgewählt aus Alkylgruppen mit 1—3 Kohlenstoffatomen, Halogen, vorzugsweise F oder Cl, Alkylengruppen mit 4—5 Kohlenstoffatomen, die Spiroverbindungen liefern, substituiert sein können, oder zwei oder vier dieser Substituenten zusammen eine oder zwei Oxogruppen



bilden, wobei R^{1a}, R^{2a}, R^{3a} und R^{4a}, wenn sie zusammen mit dem benachbarten Kohlenstoffatom im Benzimidazolring zwei Ringe bilden, miteinander kondensiert werden können, R^{5a} Wasserstoff oder eine Alkylgruppe mit 1—7 Kohlenstoffatomen ist, R^{6a} für Wasserstoff oder eine Alkylgruppe mit 1—7 Kohlenstoffatomen steht, oder R^{5a} und R^{6a} zur Bildung einer Alkenylenkette mit 3 Kohlenstoffatomen vereinigt sind, R^{7a} Wasserstoff, eine Alkylgruppe mit 1—7 Kohlenstoffatomen, eine Alkoxygruppe mit 1—7 Kohlenstoffatomen, eine Alkenyloxy- oder Alkynyloxygruppe mit jeweils 2—5 Kohlenstoffatomen ist, R^{8} für Wasserstoff oder eine Alkylgruppe mit 1—7 Kohlenstoffatomen steht, oder R^{6a} und R^{7a} oder R^{7a} und R^{8a} zusammen mit den benachbarten Kohlenstoffatomen im Pyridiniumring einen Ring bilden, worin der durch R^{6a} und R^{7a} oder R^{7a} und R^{8a} gebildete Teil —O—$(CH_2)_p$—, —$CH_2(CH_2)_p$— oder —S—$(CH_2)_p$— bedeutet, worin p für 2, 3 oder 4 steht und die O-, S- und N-Atome immer an der Position 3 in der Verbindung IIIa stehen, R eine Alkylgruppe mit 1—7 Kohlenstoffatomen, eine Cycloalkygruppe mit 3—10 Kohlenstoffatomen, eine Arylgruppe mit bis zu 10 Kohlenstoffatomen oder eine Arylalkylgruppe mit bis zu 10 Kohlenstoffatomen im Aryl und 1—7 Kohlenstoffatomen im Alkyl darstellt und $X^{\ominus}$ ein pharmazeutisch akzeptables Anion ist, gekennzeichnet durch Umsetzung unter Umwandlung und sauren Bedingungen einer Verbindung der allgemeinen Formel Ia



Ia

entweder a) säurekatalysiert oder b) nicht säurekatalysiert, zur Bildung des Salzes der Formel IIIa.

2. Verfahren nach Anspruch 1, worin das pharmazeutisch akzeptable Anion Cl^-, Br^-, I^-, PF_6 oder $AuCl_4^-$ ist.

3. Verfahren nach den Ansprüchen 1—2, worin R^{1a}, R^{2a}, R^{3a} und R^{4a} gleich oder verschieden sind und jeweils für Wasserstoff, eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen, eine Niedrigalkoxygruppe mit 1—3 Kohlenstoffatomen, Chlor, Brom, Fluor oder Jod, eine Arylgruppe mit 6 Kohlenstoffatomen, eine Aryloxygruppe mit 6 Kohlenstoffatomen, eine Aralkoxygruppe mit 6 Kohlenstoffatomen in der Arylgruppe und 1—3 Kohlenstoffatomen in der Alkoxygruppe, —COR und/oder —COOR stehen, worin R eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen, ein Cycloalkyl mit 3 Kohlenstoffatomen, ein Aryl mit 6 Kohlenstoffatomen oder eine Arylalkylgruppe mit 6 Kohlenstoffatomen in der Arylgruppe und 1—3 Kohlenstoffatomen in der Alkylgrupe ist, R^{5a} Wasserstoff oder eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen darstellt, R^{6a} Wasserstoff oder eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen ist, oder R^{6a} und R^{8a} zur Bildung einer Alkenylenkette mit 3 Kohlenstoffatomen vereinigt sind, R^{7a} Wasserstoff, eine Niedrigalkylgruppe mit 1—4 Kohlenstoffatomen, eine Alkoxygruppe mit 1—3 Kohlenstoffatomen, eine Alkenyloxy- oder eine Alkynyloxygruppe mit jeweils 3 Kohlenstoffatomen darstellt und R^{8a} Wasserstoff oder eine Niedrigalkylgruppe mit 4 Kohlenstoffatomen ist.

4. Verfahren nach den Ansprüchen 1—3, worin jedes von R^{1a}, R^{4a}, R^{5a} und R^{8a} für Wasserstoff steht, jedes von R^{2a} und R^{3a} Methyl ist, R^{7a} Methoxy bedeutet, R^{6a} Wasserstoff oder Methyl ist und X^- für BF_4^- steht.

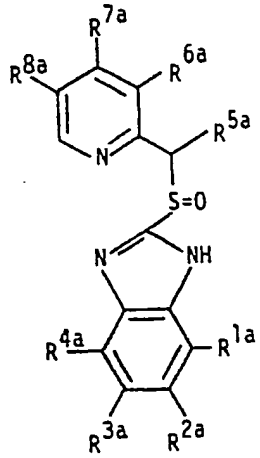
5. Verfahren nach den Ansprüchen 1—3, worin jedes von R^{1a}, R^{3a}, R^{4a} und R^{5a} Wasserstoff ist, jedes von R^{6a} und R^{8a} Methyl darstellt, R^{7a} Methoxy bedeutet, R^{2a} Wasserstoff oder Methoxy ist und X^- für PF_6^- oder $AuCl_4^-$ steht.

6. Verfahren nach Anspruch 1, worin die Isomerenmischung von 2,4 - Dimethyl - 3,9 - dimethoxy - 5*H* - pyrido - [1',2':4,5] - [1,2,4] - thiadiazino - [2,3 - a] - benzimidazol - 13 - ium - tetraflu rb rat und 2,4 - Dimethyl - 2,10 - dimethoxy - 5*H* - pyrido - [1',2':4:5] - [1,2,4] - thiadiazino - [2,3 - a] - benzimidazol - 13 - ium - tetrafluorborat.

7. Verfahren nach Anspruch 1, worin die Reaktion mit einer Säure katalysiert wird.

8. Verfahren nach Anspruch 1 und 7, worin die Reaktion mit HPF_6, HBF_4 oder $HAuCl_4$ katalysiert wird.

9. Verfahren nach Anspruch 1, worin eine Verbindung der allgemeinen Formel Ia



Ia

worin R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{7a} und R^{8a} wie in Anspruch 1 definiert sind und R^{5a} und R^{6a} unter Bildung einer Alkenylenkette mit 3 Kohlenstoffatomen vereinigt sind, als Ausgangsverbindung eingesetzt wird.

10. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, die als aktives Ingrediens eine Verbindung nach einem der Ansprüche 1—6 enthält, dadurch gekennzeichnet, daß die aktive Verbindung der Formel IIIa mit einem oder mehreren Trägern zu einer pharmazeutischen Zusammensetzung vermischt wird.

11. Verfahren nach einem der Ansprüche 1—8, worin die erhaltene Verbindung zur Verwendung bei der Magensäureinhibition bei Säugetieren und Menschen bestimmt ist.

12. Verfahren nach einem der Ansprüche 1—8, worin die erhaltene Verbindung zur Verwendung als gastrointestinales zellschützendes Mittel bei Säugetieren und Menschen bestimmt ist.

13. Verfahren nach einem der Ansprüche 1—8, worin die erhaltene Verbindung zur Verwendung bei der Behandlung von gastrointestinalen Entzündungserkrankungen bei Säugetieren und Menschen bestimmt ist.

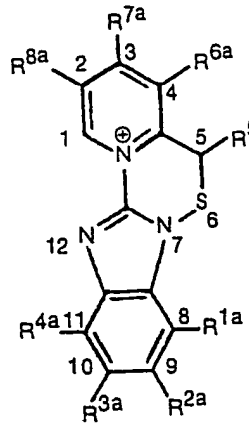
14. Verwendung einer Verbindung der allgemeinen Formel IIIa nach Anspruch 1 zur Herstellung einer pharmazeutischen Präparation zur Inhibition von Magensäuresekretion.

15. Verwendung einer Verbindung der allgemeinen Formel IIIa nach Anspruch 1 zur Herstellung einer pharmazeutischen Präparation zur Behandlung von gastrointestinalen Entzündungserkrankungen.

16. Verwendung einer Verbindung der allgemeinen Formel IIIa nach Anspruch 1 zur Herstellung einer pharmazeutischen Präparation mit gastrointestinaler Zellschutzwirkung.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé de formule IIIa



IIIa

dans laquelle R^{1a}, R^{2a}, R^{3a} et R^{4a} sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 7 atomes de carbone, un groupe alcoxy ayant 1 à 7 atomes de carbone et éventuellement substitué par du fluor ou du chlore, un halogène, —CN, —CF_3, —NO_2, —COR, —COOR, un groupe aryle ayant jusqu'à 10 atomes de carbone, un groupe aryloxy ayant jusqu'à 10 atomes de carbone, un groupe arylalcoxy ayant jusqu'à 10 atomes de carbone dans le groupe aryle et 1 à 7 atomes de carbone dans le groupe alcoxy, ou bien les groupes adjacents R^{1a}, R^{2a}, R^{3a} et R^{4a} forment, avec les atomes de carbone adjacents du noyau benzimidazole, un noyau monocyclique à 5, 6 ou 7 chaînons, ces noyaux pouvant être saturés ou insaturés et pouvant contenir 0 à 3 hétéro-atomes choisis parmi N et O, et ces noyaux pouvant éventuellement être substitués par 1 à 4 substituants choisis parmi des groupes alkyles ayant 1 à 3 atomes de carbone, un halogène, de préférence F ou Cl, des radicaux alkylène contenant 4—5 atomes de carbone en donnant des composés spiro, ou bien deux ou quatre de ces substituants forment, ensemble un ou deux groupes oxo

et si R^{1a}, R^{2a}, R^{3a} et R^{4a}, forment avec les atomes de carbone adjacents du noyau benzimidazole, deux noyaux, ceux-ci peuvent être condensés l'un sur l'autre; R^{5a} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 7 atomes de carbone; R^{6a} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 7 atomes de carbone, ou bien R^{5a} et R^{6a} sont reliés l'un à l'autre pour former une chaîne alcénylène ayant 3 atomes de carbone, R^{7a} représente un atome d'hydrogène, un groupe alkyle ayant 1 à 7 atomes de carbone, un groupe alcoxy ayant 1 à 7 atomes de carbone, un groupe alcényloxy ou alcynyloxy ayant chacun 2 à 5 atomes de carbone, R^{8} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 7 atomes de carbone, ou bien R^{6a} et R^{7a}, ou R^{7a} et R^{8a}, forment, avec les atomes de carbone adjacents du noyau pyridinium, un noyau dans lequel la partie constituée par R^{6a} et R^{7a} ou par R^{7a} et R^{8a} est —O—$(CH_2)_p$—, —$CH_2(CH_2)_p$— ou —S—$(CH_2)_p$—, où p vaut 2, 3 ou 4 et les atomes de O, S et N sont toujours fixés en position 3 dans le composé IIIa, R représente un groupe alkyle ayant 1 à 7 atomes de carbone, un groupe cyclo-alkyle ayant 3 à 10 atomes de carbone, un groupe aryle ayant jusqu'à 10 atomes de carbone ou un groupe arylalkyle ayant jusqu'à 10 atomes de carbone dans la partie aryle et ayant 1 à 7 atomes de carbone dans la partie alkyle, et $X^{\ominus}$ est un anion pharmaceutiquement acceptable.

2. Composé selon la revendication 1, dans lequel l'anion pharmaceutiquement acceptable est Cl^-, Br^-, I^-, PF_6^- ou $AuCl_4^-$.

3. Composé selon les revendications 1—2, dans lequel R^{1a}, R^{2a}, R^{3a} et R^{4a} sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle inférieur ayant 1 à 4 atomes de carbone, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un atome de chlore, de brome, de fluor ou d'iode, un groupe aryle ayant 6 atomes de carbone, ou groupe aryloxy ayant 6 atomes de carbone, un groupe aralcoxy ayant 6 atomes de carbone dans le groupe aryle et 1 à 3 atomes de carbone dans le groupe alcoxy, —COR et/ou —COOR, où R est un groupe alkyle inférieur ayant 1 à 4 atomes de carbone, un groupe cycloalkyle ayant 3 atomes de carbone, un groupe aryle ayant 6 atomes de carbone ou un groupe arylalkyle ayant 6 atomes de carbone dans le groupe aryle et 1 à 3 atomes de carbone dans le groupe alkyle, R^{5a} représente un atome d'hydrogène ou un groupe alkyle inférieur ayant 1 à 4 atomes de carbone, R^{6a} est un atome d'hydrogène ou un groupe alkyle inférieur ayant 1 à 4 atomes de carbone ou bien R^{5a} et R^{6a} sont reliés ensemble pour former une chaîne alcénylène ayant 3 atomes de carbone, R^{7a} est un atome

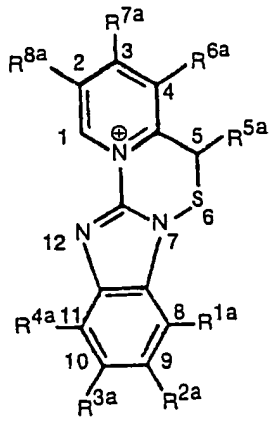
d'hydrogène, un groupe alkyle inférieur ayant 1 à 4 atomes de carbone, un groupe alcoxy ayant 1 à 3 atomes de carbone, un groupe alcényloxy ou alcynyloxy ayant chacun 3 atomes de carbone et R^{8a} représente un atome d'hydrogène ou un groupe alkyle inférieur ayant 4 atomes de carbone.

4. Composé selon les revendications 1 à 3, dans lequel chacun des symboles R^{1a}, R^{4a}, R^{5a} et R^{8a} représente un atome d'hydrogène, chacun des symboles R^{2a} et R^{3a} représente un groupe méthyle, R^{7a} représente un groupe méthoxy, R^{6a} représente un atome d'hydrogène ou un groupe méthyle, et X^- représente BF_4^-.

5. Composé selon les revendications 1 à 3, dans lequel chacun des symboles R^{1a}, R^{3a}, R^{4a} et R^{5a} représente un atome d'hydrogène, chacun des symboles R^{6a} et R^{8a} représente un groupe méthyle, R^{7a} représente un groupe méthoxy, R^{2a} représente un atome d'hydrogène ou un groupe méthoxy et X^- représente PF_6^- ou $AuCl_4^-$.

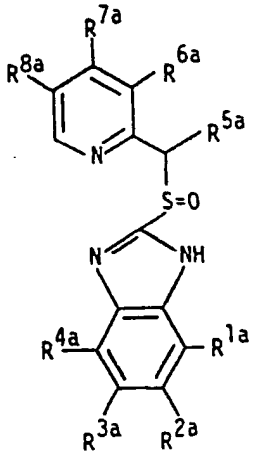
6. Mélange isomère du tétrafluoroborate de 2,4-diméthyl-3,9-diméthoxy-5*H*-pyrido-[1',2':4,5][1,2,4]-thiadiazino[2,3-a]benzimidazol-13-ium et du tétrafluoroborate de 2,4-diméthyl-3,10-diméthoxy-5*H*-pyrido-[1',2':4:5][1,2,4]-thiadiazino[2,3-a]benzimidazol-13-ium.

7. Procédé pour la préparation d'un composé de formule IIIa



IIIa

dans laquelle R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a} et R^{8a} ainsi que $X^{\ominus}$ sont tels que définis à la revendication 1, caractérisé en ce qu'on fait réagir, dans des conditions de transformation et en milieu acide, un composé de formule générale Ia



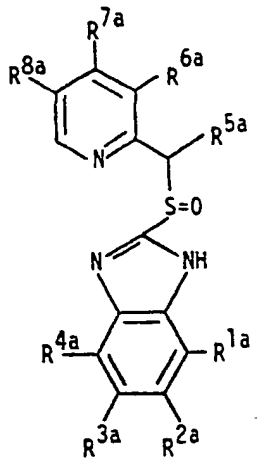
Ia

a) avec catalyse acide ou b) sans catalyse acide, pour former le sel de formule IIIa.

8. Procédé selon la revendication 7, dans lequel la réaction est catalysée par un acide.

9. Procédé selon les revendications 7 ou 8, dans lequel la réaction est catalysée par HPF_6, HBF_4 ou $HAuCl_4$.

10. Composé de formule général Ia



Ia

dans laquelle R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{7a} et R^{8a} sont tels que définis à la revendication 1, et R^{5a} et R^{6a} sont reliés l'un à l'autre avec formation d'une chaîne alcénylène ayant 3 atomes de carbone.

11. Composition pharmaceutique, contenant comme ingrédient actif un composé selon l'une quelconque des revendications 1 à 6.

12. Composé tel que défini dans l'une quelconque des revendications 1 à 6, destiné à servir à inhiber la sécrétion des acides gastriques chez les mammifères et l'être humain.

13. Composé tel que défini dans l'une quelconque des revendications 1 à 6, destiné à servir d'agent de cytoprotection gastro-intestinale cnez les mammifères et l'être humain.

14. Composé tel que défini dans l'une quelconque des revendications 1 à 6, destiné à servir au traitement de maladies inflammatoires gastro-intestinales chez les mammifères et l'être humain.

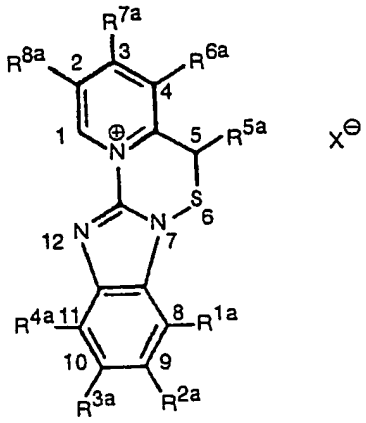
15. Utilisation d'un composé de formule générale IIIa selon la revendication 1 pour la fabrication d'une préparation pharmaceutique pour inhiber la sécrétion des acides gastriques.

16. Utilisation d'un composé de formule générale IIIa selon la revendication 1 pour la fabrication d'une préparation pharmaceutique pour le traitement de maladies inflammatoires gastro-intestinales.

17. Utilisation d'un composé de formule générale IIIa selon la revendication 1 pour la fabrication d'une préparation pharmaceutique ayant un effet cytoprotecteur gastro-intestinal.

Revendications pour l'Etat contractant: AT

1. Procédé pour la préparation d'un composé de formule IIIa



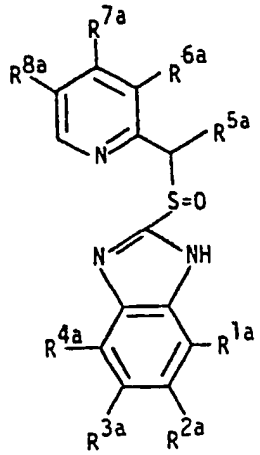
IIIa

dans laquelle R^{1a}, R^{2a}, R^{3a} et R^{4a} sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 7 atomes de carbone, un groupe alcoxy ayant 1 à 7 atomes de carb ne, éventuellement substitué par du fluor ou du chlore, un halogène, —CN, —CF_3, —NO_2, —COR, —COOR, un groupe aryle ayant jusqu'à 10 atomes de carbone, un groupe aryloxy ayant jusqu'à 10 atomes de carbone ou un groupe aryloxy ayant jusqu'à 10 atomes de carbone dans le groupe aryle et 1 à 7 atomes

de carbone dans le groupe alcoxy, ou bien les groupes adjacents R^{1a}, R^{2a}, R^{3a} et R^{4a} forment, avec les atomes de carbone adjacents du noyau benzimidazole, un noyau monocyclique à 5, 6 ou 7 chaînons, ces noyaux pouvant être saturés ou insaturés et pouvant contenir 0 à 3 hétéro-atomes choisis parmi N et O, et ces noyaux pouvant être éventuellement substitués par 1 à 4 substituants choisis parmi des groupes alkyles ayant 1 à 3 atomes de carbone, un halogène, de préférence F ou Cl, des radicaux alkylène contenant 4—5 atomes de carbone en donnant des composés spiro, ou bien deux ou quatre de ces substituants forment, ensemble un ou deux groupes oxo

$$(-\overset{\overset{O}{\|}}{C}-),$$

et si R^{1a}, R^{2a}, R^{3a} et R^{4a}, forment avec les atomes de carbone adjacents du noyau benzimidazole, deux noyaux, ceux-ci peuvent être condensés l'un sur l'autre; R^{5a} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 7 atomes de carbone, R^{6a} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 7 atomes de carbone, ou bien R^{5a} et R^{6a} sont reliés l'un à l'autre pour former une chaîne alcénylène ayant 3 atomes de carbone, R^{7a} représente un atome d'hydrogène, un groupe alkyle ayant 1 à 7 atomes de carbone, un groupe alcoxy ayant 1 à 7 atomes de carbone, un groupe alcényloxy ou alcynyloxy ayant chacun 2 à 5 atomes de carbone, R^{8} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 7 atomes de carbone, ou bien R^{6a} et R^{7a}, ou R^{7a} et R^{8a}, forment, avec les atomes de carbone adjacents du noyau pyridinium, un noyau dans lequel la partie constituée par R^{6a} et R^{7a} ou par R^{7a} et R^{8a} est $-O-(CH_2)_p-$, $-CH_2(CH_2)_p-$ ou $-S-(CH_2)_p-$, où p vaut 2, 3 ou 4, et les atomes de O, S et N sont toujours fixés en position 3 dans le composé IIIa, R représente un groupe alkyle ayant 1 à 7 atomes de carbone, un groupe cyclo-alkyle ayant 3 à 10 atomes de carbone, un groupe aryle ayant jusqu'à 10 atomes de carbone ou un groupe arylalkyle ayant jusqu'à 10 atomes de carbone dans le fragment aryle et ayant 1 à 7 atomes de carbone dans le fragment alkyle, et $X^{\ominus}$ est un anion pharmaceutiquement acceptable, procédé caractérisé en ce qu'on fait réagir, dans des conditions de transformation et en milieu acide, un composé de formule générale Ia



Ia

a) avec catalyse acide ou b) sans catalyse acide, pour former le sel de formule IIIa.

2. Procédé selon la revendication 1, dans lequel l'anion pharmaceutiquement acceptable est Cl^-, Br^-, BF_4, PF_6^- ou $AuCl_4^-$.

3. Procédé selon les revendications 1—2, dans lequel les symboles R^{1a}, R^{2a}, R^{3a} et R^{4a} sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle inférieur ayant 1 à 4 atomes de carbone, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un atome de chlore, de brome, de fluor ou d'iode, un groupe aryle ayant 6 atomes de carbone, ou groupe aryloxy ayant 6 atomes de carbone, un groupe aralcoxy ayant 6 atomes de carbone dans le fragment aryle et 1 à 3 atomes de carbone dans le fragment alcoxy, —COR et/ou —COOR, où R est un groupe alkyle inférieur ayant 1 à 4 atomes de carbone, un groupe cyclo-alkyle ayant 3 atomes de carbone, un groupe aryle ayant 6 atomes de carbone ou un groupe arylalkyle ayant 6 atomes de carbone dans le fragment aryle et 1 à 3 atomes de carbone dans le fragment alkyle, R^{5a} représente un atome d'hydrogène ou un groupe alkyle inférieur ayant 1 à 4 atomes de carbone, R^{6a} représente un atome d'hydrogène ou un groupe alkyle inférieur ayant 1 à 4 atomes de carbone, ou bien R^{5a} et R^{6a} sont reliés l'un à l'autre pour former une chaîne alcénylène ayant 3 atomes de carbone, R^{7a} représente un atome d'hydrogène, un groupe alkyle inférieur ayant 1 à 4 atomes de carbone, un groupe alcoxy ayant 1 à 3 atomes de carbone, un groupe alcényloxy ou alcynyloxy ayant chacun 3 atomes de carbone, et R^{8a} représente un atome d'hydrogène ou un groupe alkyle inférieur ayant 1 à 4 atomes de carbone.

4. Procédé selon les revendications 1 à 3, dans lequel chacun des symboles R^{1a}, R^{4a}, R^{5a} et R^{8a} représente un atome d'hydrogène, chacun des symboles R^{2a} et R^{3a} est un groupe méthyle, R^{7a} représente un groupe méthoxy, R^{6a} est un atome d'hydrogène ou un groupe méthyle, et X^- représente BF_4^-.

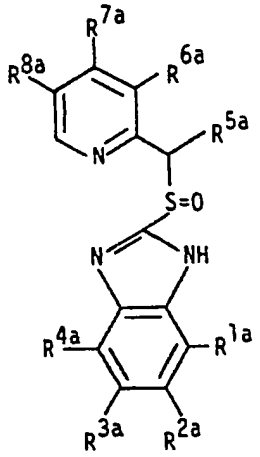
5. Procédé selon les revendications 1 à 3, dans lequel chacun des symboles R^{1a}, R^{3a}, R^{4a} et R^{5a} représente un atome d'hydrogène, chacun des symboles R^{6a} et R^{8a} représente un groupe méthyle, R^{7a} représente un groupe méthoxy, R^{2a} représente un atome d'hydrogène ou un groupe méthoxy et X^- représente PF_6^- ou $AuCl_4^-$.

6. Procédé selon la revendication 1, dans lequel on prépare le mélange isomère du tétrafluoroborate de 2,4-diméthyl-3,9-diméthoxy-5*H*-pyrido-[1',2':4,5][1,2,4]-thiadiazino[2,3-a]benzimidazol-13-ium et du tétrafluoroborate de 2,4-diméthyl-3,10-diméthoxy-5*H*-pyrido-[1',2':4,5][1,2,4]-thiadiazino[2,3-a]benzimidazol-13-ium.

7. Procédé selon la revendication 1, dans lequel la réaction est catalysée par un acide.

8. Procédé selon les revendications 1 et 7, dans lequel la réaction est catalysée par HPF_6, HBF_4 ou $HAuCl_4$.

9. Procédé selon la revendication 1, dans lequel on utilise comme composé de départ un composé de formule générale la



Ia

dans laquelle R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{7a} et R^{8a} sont tels que définis à la revendication 1 et R^{5a} et R^{6a} sont reliés l'un à l'autre avec formation d'une chaîne alcénylène ayant 3 atomes de carbone.

10. Procédé pour la préparation d'une composition pharmaceutique contenant comme ingrédient actif un composé selon l'une quelconque des revendications 1 à 6, caractérise en ce qu'on mélange le composé actif de formule IIIa avec un ou plusieurs excipients pour obtenir une composition pharmaceutique.

11. Procédé selon l'une quelconque des revendications 1 à 8, dans lequel le composé obtenu est destiné à servir à inhiber la sécrétion des acides gastriques chez les mammifères et l'être humain.

12. Procédé selon l'une quelconque des revendications 1 à 8, dans lequel le composé obtenu est destiné à servir d'agent cytoprotecteur gastro-intestinal chez les mammifères et l'être humain.

13. Procédé selon l'une quelconque des revendications 1 à 8, dans lequel le composé obtenu est destiné au traitement des maladies inflammatoires gastro-intestinales chez les mammifères et l'être humain.

14. Utilisation d'un composé de formule générale IIIa selon la revendication 1 pour la fabrication d'une préparation pharmaceutique destinée à inhiber la sécrétion des acides gastriques.

15. Utilisation d'un composé de formule générale IIIa selon la revendication 1 pour la fabrication d'une préparation pharmaceutique destinée au traitement de maladies inflammatoires gastro-intestinales.

16. Utilisation d'un composé de formule générale IIIa selon la revendication 1 pour la fabrication d'une préparation pharmàceutique ayant un effet cytoprotecteur gastro-intestinal.